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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/766,057
Filing Date: January 28, 2004
Appellant(s): LARSEN ET AL.

Jan N. Tittel, Ph.D.
Reg. No. 52,290
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/6/11 appealing from the Office action mailed 8/4/10.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 18 and 25-35.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6,093,382	Wedeking et al.	07-2000
EP0282057	Sinkule et al.	10-1988

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18 and 25-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wedeking et al. (US 6,093,382) in view of Sinkule et al. (EP 282057).

Wedeking et al. (US 6,093,382) discloses the method of preparing a diagnostic/therapeutic gadolinium-folate (folic acid) conjugate and the method of targeting the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate to a tumor cell expressing FBP (folate binding protein) (i.e. malignant cells) which involves administering the conjugate to a mammal and monitoring the biodistribution (column 1,

lines 8-50; column 6, lines 28+; column 7, lines 21-28 and 48-59; column 8, line 44-59; column 10, lines 18-25; column 68, lines 31+; example 17). The compound of column 51-52 contains multiple folates (folic acid) conjugated to a radionuclide chelator capable of binding gadolinium. FBP is frequently strikingly elevated in a variety of carcinomas and thus allows for selective concentration of pharmaceutical or diagnostic agents in tumor cells, such as ovarian cancer relative to normal cells (column 3, lines 25-35; column 4, lines 37-54; column 5, lines 1-7). The monomeric folate conjugates of Gd chelates designed for use in MR applications indicate that structural modifications that bring about an increase in the intensity of the MR signal are advantageous, as the signal intensity obtainable with this technique is determined by the quantity of paramagnetic or superparamagnetic metal that can be localized in the target tissues which is limited by the quantity of folate binding protein present in those tissue (column 7, lines 21-38). Wedeking et al. does not disclose the coupling of an antibody to the folate gadolinium-folate (folic acid) conjugate.

Sinkule et al. (EP 282057) discloses the method of monitoring the biodistribution of a receptor binding conjugate comprising three components, 1.) a monoclonal antibody, IgG (column 2, lines 30-31; example 4), 2.) a radionuclide (column 3, lines 39-55; column 17, lines 5-17) a chemotherapeutic agent, such as folate analogues and multiples thereof (abstract; column 2, lines 11-14 and 29-30; column 4, lines 18-28) via the administration to a mammalian subject (i.e. intravenous) (column 6, lines 19+). The method of linking the folic acid derivative to an antibody involves conversion of the folic acid derivative to the activated ester (mixed anhydride) with acetic anhydride and mixing

it with the antibody (column 8, lines 40-44). The antibody-folic acid derivative product is further attached to a radionuclide (column 6, lines 22-25). The antibody may be a monoclonal, polyclonal or variations thereof used for a wide variety of target antigens (column 3, lines 56+; column 4, lines 9-15), such as (443A6) which recognize a 40k dalton epithelial antigen found on human breast adenocarcinomas (column 8, lines 33-39; example 3). The targeting antibodies are included in the conjugate to target the conjugate to a desired tumor cell for uptake with a high degree of specificity which facilitates the destruction of cancerous cells while minimizing the damage to normal cells (column 5, lines 9-12 and 22-47) an the choice of antibody will depend on the type of cancer with which the patient is afflicted (column 5, lines 40-47).

At the time of the invention it would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Sinkule et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing the damage to normal cells.

The IgG of the disclosure encompasses the IgG antibody of the instant claims and therefore is capable of the same functions, such as not interfering with the targeting of folate and has the same properties.

(10) Response to Argument

Appellant asserts that the cited art fails to describe targeting the conjugate to a malignant cell using the folate component of a complex, and that, instead, Sinkule explicitly states that the antibody component targets the complex to the tumor and that the folic acid analogues of Sinkule are described as chemotherapeutic agents. The folic acid analogue forms part of the "therapeutic activity" of the conjugate that is localized to the antibody. Sinkule does not teach or suggest folate targeting. Given that, in Sinkule, the antibody is targeting the complex, one simply cannot conclude that the presence of the antibody does not interfere with folate targeting. On this point, Appellants direct the office's attention to knowledge in the art (Shinoda) showing that adding a large molecule, such as BSA, to a folate-containing complex can interfere with the targeting ability of the folate. BSA (a large protein with a mass of about 66,000 amu) on folate targeting is relevant to what one of skill in the art would expect to observe if another large protein (e.g. IgG antibody) is coupled to a folate-targeted complex. Appellants submit that, in view of Shinoda, one skilled in the art would not have considered that a large molecule, like an antibody, could be complexed with a folate with the expectation that the folate would maintain its targeting ability.

The reference of Sinkule was not used to teach of the non-cytotoxic folate of the instant claims but was used to teach that an antibody (e.g. IgG) can be coupled to a folate analogue via conversion of the folic acid derivative to the activated ester (mixed anhydride) with acetic anhydride and mixing it with the antibody. The antibody-folic acid derivative product is further attached to a radionuclide for the method of monitoring the

biodistribution of a receptor binding conjugate. Further, the instant claims do not exclude that the non-cytotoxic folate is a chemotherapeutic agent. All pharmaceuticals, chemical agents, drugs, etc. may be cytotoxic in excess.

The reference of Wedeking was used to teach of the gadolinium-folate (folic acid) conjugate wherein the folate (folic acid) is a folate receptor-binding ligand that is capable of enhancing the transport of the radioactive metal across the membranes of living cells. The conjugate is used for the method of targeting the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate to a tumor cell expressing FBP (folate binding protein). Wedeking teaches that "to increase the Gd at the folate site in vivo it is also possible to incorporate Gd chelate into naturally occurring or unnatural amino acids, peptides, etc."

The instant claims do not recite targeting/binding the conjugate to a malignant cell via the non-cytotoxic folate component and antibody exactly at the same time but recites that the antibody has affinity for the tumor associated antigen and the conjugate is a dual binding conjugate. Therefore, the instant claims include binding of one of the antibody (such as to the tumor associated antigen) or binding of the non-cytotoxic folate (such as to the folate binding protein) individually at any given time. The IgG antibody of the disclosure encompasses the IgG of the instant claims, has the same properties and is capable of the same functions and thus, should not interfere with folate targeting.

The instant claims do not recite, “that the non-cytotoxic folate component targets folate binding protein” but states that the cell expresses a tumor associated antigen and expresses folate binding protein.

Therefore, at the time of the invention it would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Sinkule et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing the damage to normal cells.

Also, the comparison of the BSA molecule is not a direct correlation of the binding of the IgG antibody as they have different structures (i.e. folding), properties, etc. and molecular weight does not specifically have an effect on the binding characteristics of the IgG.

Appellant asserts that the Office's reliance on the inherency that the "IgG of Sinkule et al. encompasses the IgG antibody of the instant claims and therefore is capable of the same functions, such as not interfering with the targeting of folate and has the same properties” is incorrect.

The instant claims do not recite targeting/binding the conjugate to a malignant cell via the non-cytotoxic folate component and antibody exactly at the same time but recites that the antibody has affinity for the tumor associated antigen and the conjugate

is a dual binding conjugate. Therefore, the instant claims include binding of one of the antibody or non-cytotoxic folate individually. The IgG has specific folding and binding properties and the folate has specific binding properties. The addition of IgG does not alter folates inherent binding properties.

Appellant asserts that Wedeking describes targeting of small molecules using a folate. Even when larger complexes of multiple chelating agents are used and several folates are required the molecular weight is fairly low. The office does not appear to distinguish an antibody from a small molecular moiety. IgG is thirty times larger than the largest complexes of Wedeking and three orders of magnitude larger than a folate. Given the vast size differences between a folate and an antibody, folate targeting and antibody targeting cannot simply be treated as if they are equivalent. Nothing in the combination of Wedeking with Sinkule teaches or suggests that the vanishingly small folate moiety (relative to an antibody) can have any useful positive effect in altering the distribution of a massive antibody or, conversely, that including an antibody in a complex, such as that of Wedeking, that is targeted using a folate does not interfere with targeting by that folate.

Wedeking teaches that “to increase the Gd at the folate site in vivo it is also possible to incorporate Gd chelate into naturally occurring or unnatural amino acids, peptides, etc.” The reference of Sinkule teaches of conjugates comprising a folate analogue bound to an antibody for localization in vivo of the conjugate. The Examiner does not assert that folate targeting and antibody targeting are equivalent but asserts that the folate (folic acid) folate binding ligand of Wedeking has targeting/binding

capabilities toward cells comprising folate binding protein. The examiner asserts that the antibody of Sinkule has targeting/binding capabilities to target antigens and doesn't alter the binding capabilities of folate. The reference of Sinkule does not exclude simultaneous and/or synergistic folate targeting/binding.

At the time of the invention it would have been obvious to one ordinarily skilled in the art to attach an antibody, such as the IgG of Sinkule et al. to the diagnostic/therapeutic gadolinium-folate (folic acid) conjugate of Wedeking et al. to target the conjugate specifically to a desired type of cancer cells/target. FBP is expressed in normal as well as different tumor cells and thus it would be advantageous to attach an antibody to the conjugate of Wedeking et al. to ensure site-specific targeting of the conjugate into the desired tumor cells with enhanced affinity while minimizing the damage to normal cells.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michael G. Hartley/

Supervisory Patent Examiner, Art Unit 1618

Conferees:

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627

/Melissa Perreira/

Examiner, Art Unit 1618